Incorporating Genomic Information into Personalized Care

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ersonal genomic information is poised to revolutionize medicine and provide patients with increasingly individualized medical care. Advances in genomic typing and sequencing technologies are making access to inexpensive, personal genomic information a rapidly evolving reality. However, the effective integration of genomic information into clinical care will pose many logistical, ethical, and legal challenges moving forward. In response to this rapidly evolving health care revolution, the U.S. Air Force (USAF) has established the Patient-Centered Precision Care Research (PC2-Z) Program. The aim of this program is to evaluate the clinical impact of genome-informed care and to begin to lay the foundation for its implementation in the USAF. The PC2-Z program’s overarching goal is to gather clinical knowledge and provide recommendations for translating genome-informed medicine into personalized health care for DoD personnel and beneficiaries. APL is serving as the program integrator for this ground-breaking program, bringing together the government, academic, and industry partners to implement program focus areas in research, bioinformatics, education, and policy. A centerpiece of the program is a study enrolling active duty volunteers from the Air Force Medical Service to evaluate the utility of their genomic information and its effect on their personalized care and on their behavior. The data, evidence, and infrastructure developed in the PC2-Z program are also planned to be implemented by the sister services.

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If asked about the upcoming revolution in “personalized medicine,” many primary care physicians will tell you that medicine has always been tailored to the individual. Although this is true, research evidence and
technology are advancing rapidly and are beginning to enable precisely tailored, personalized medicine using advanced tools in genomics, systems biology, and bioinformatics. These tools and knowledge hold promise to deliver greater predictability of both rare and complex diseases for any individual, especially when used in a comprehensive system with family histories, lifestyle data, and normal medical data.

Many have been asking why genome-informed, personalized medicine has not made its way into the clinic. The publication of the draft human genome sequence in 2001 seemed to provide a road map to characterizing human disease; however, the reality was that this genome represented a single individual. Much of the hereditability of genetic diseases is found in the variation between individual genomes. To identify these variations, geneticists had to characterize the genomes of many different individuals among many different populations. The majority of this work was done with genotyping technologies such as SNP chips, which categorized single-nucleotide polymorphisms (SNPs) found genome-wide. The resulting data also led to the use of SNP-genotyping technologies for looking at groups of people with chronic diseases in an attempt to infer whether any SNPs in their genomes could be associated with the chronic disease when compared with similar control groups with no such disease. This type of effort, called a genome-wide association study (GWAS), has been widely implemented and has resulted in SNPs being associated with many different conditions. To date, nearly 1500 GWASs have been done on diseases, traits, and complex conditions. A list of these associations and their locations on each of the 23 chromosomes is represented in Fig. 1. Today there are several direct-to-consumer (DTC) genomic companies that offer SNP chip genetic screening for many of these conditions and traits; however, the predictive value of SNPs for most conditions is small. In addition, some of the DTC data may offer conflicting results, and the use of DTC-determined genomic information has not been evaluated in a clinical setting.

The low predictive power of SNPs for complex diseases is an important issue. Only a few conditions, such as macular degeneration, have associated SNPs that account for a large amount of the genetic heritability (50% in the case of macular degeneration, measured by the recurrence risk among siblings). This missing heritability for complex diseases will probably be found in other risk factors such as non-SNP genetic variants, lifestyle choices, and environmental factors such as job-related exposures.

Interestingly, the plummeting cost of sequencing is making possible the identification of non-SNP structural variants such as copy-number variants, insertions, and deletions, and it is widely anticipated that individual genomes will be able to be sequenced in Clinical Laboratory Improvement Amendments-certified laboratories for a cost of under $1000 in the next few years. This will provide a wealth of information to the research community for new association studies, which will provide better predictive value to individuals for complex diseases. In addition, personalized genome sequencing information will become readily available. When it does, the revolution in genome-informed, personalized care will be well under way, and the infrastructure and evidence to support this revolution needs to be anticipated now.

**PC2 PROGRAM OVERVIEW**

Ultimately, any implementation of personalized medicine will have to include not just genomics but also the use of all available medical data and risk factors such as family history, lifestyle, and environmental characteristics. The U.S. Air Force (USAF) Office of the Surgeon General recently established the Patient-Centered Precision Care Research (PC2-Z) Program to gather evidence and provide recommendations for translating genome-informed medicine into personalized health care and to ultimately provide state-of-the-art care for DoD personnel and beneficiaries. The effort is supported by congressional interest in integrating genome-informed medicine.

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**Figure 1.** Published genome-wide associations through June 2011 from the National Human Genome Research Institute Catalog of Published Genome-Wide Association Studies (www.genome.gov/GWAStudies), which contains 1449 published genome-wide associations at p ≤ 5 × 10⁻⁸ for 237 traits. (a) The virtual karyotype: A graphic representation of all chromosomes in the human genome, containing locations for each complex trait determined by a GWAS. Colored circles represent variant associations from a GWAS for conditions shown in panel b. A GWAS attempts to determine an association between an allele such as an SNP and a cohort of individuals with a particular disease condition or trait. Population stratification is done to minimize structural variations common to specific ethnic groups and increase power. For a typical GWAS, alleles are determined to be significant if they are in linkage disequilibrium, which is the nonrandom occurrence in a population of an allele at two or more sites based on their frequencies. (For a GWAS, linkage disequilibrium is considered significant provided an r² ≥ 0.8.) Frequencies are usually based on International HapMap data that used a minor allele frequency >5%, where minor allele frequency is the frequency at which the less common allele occurs in the population. Once determined to be in linkage disequilibrium, an odds ratio can be calculated that represents the probability of disease for the group with the variant. For this study, relative risk, which represents the ratio of disease risk in the group with the allele to the risk of disease in the group without the allele, is calculated. (Reproduced with permission from Ref. 11.)
medicine across the DoD, which has the population and numbers to demonstrate evidence that will support the advancement of genomic research translated into clinical practice. The PC2 program is composed of two main components: PC2-Z (research), which performs genomic and personalized medicine research, and PC2-C (applied clinical epidemiology), which is the transitional program that will apply the lessons learned and the infrastructure developed from PC2-Z.

PC2-Z is being driven by the increasing availability of genomic data resulting in the ability to collaboratively leverage a wide range of research efforts in government, academia, and industry to shift to evidence-based care. The conceptual structure of the PC2-Z program is shown in Fig. 2. The Air Force Medical Service (AFMS) program chief relies on APL as the system integrator. In this role, APL leads the program by establishing program concepts, conducting research, performing system engineering, developing performance specifications, and overseeing other organizations performing technical tasks related to the program. The focus of this program is not to establish a stand-alone effort but to partner and collaborate with existing, outstanding research institutions that are conducting the leading research in this field. The PC2-Z program has developed partnerships between Air Force Medicine, APL, Coriell Institute for Medical Research, the Duke Institute for Genome Sciences and Policy, and the National Institutes of Health.

To ensure the overarching purpose of the PC2-Z program is achieved, a comprehensive program approach (Fig. 2) is used that follows four major pillars:

- **Research/knowledge generation:** The research/knowledge generation effort will provide overall research to assess the clinical utility of the genomic information in the delivery of health care, which includes implementation of a PC2-Z clinical utility study (CUS). In addition, research infrastructure such as a biobank will be implemented and ancillary studies will be initiated on topics of interest to the DoD.

- **Bioinformatics/clinical systems engineering:** This effort will provide research and test bed development to address the major challenges to implementation, management, security, and maintenance of personalized medicine data and health record systems. A prototype advanced genomics diagnostic system will be developed that will provide overall information management and provide virtual clinical decision support to the AFMS.

- **Ethical, legal, and social issues (ELSIs)/policy research:** ELSIs need to be identified and addressed before genomic information can be used in a clinical environment. The ELSI/policy effort for PC2-Z seeks to bring together stakeholders, identify important ELSIs and efforts to address them, and implement solutions/best practices into the PC2 program.

- **Education and coordination:** This effort will seek to identify and leverage information and educational material for the health care community and the general public, addressing the current gap in patient and provider proficiency in genomic medicine. Program-specific material (e.g., websites, newsletters, etc.) are being generated, and partnerships with existing organizations and efforts are being leveraged.

**PC2-Z CUS**

At the heart of the PC2-Z program is a CUS to evaluate the impact of genome-informed health care on participant health, behavior, and health care utilization. This study (F-WR-2011-0046) was approved by the USAF Wright-Patterson Institutional Review Board in January 2012 and is currently enrolling active duty vol-

![Figure 2. Programmatic overview of the PC2-Z program. APL serves as the program integrator, bringing together leadership, advisory boards, and consortium team members. There are four pillar thrust areas, and values that enable execution and later implementation within the broader community provide the foundation for the program.](image-url)
SNP variants from the human genome. Genomic information is coupled with an analysis of the volunteer’s medical history and family history to create a personalized medicine profile (Fig. 3). This profile reports risk for clinically actionable, common complex diseases that are traditionally treated in the primary care setting, such as type 2 diabetes, and the profile, along with genetic counseling as needed, is provided to the CUS participant. Participants will be followed longitudinally over several years to evaluate the effect of genome-informed risk on health (e.g., earlier detection of disease that reduces morbidity), behavior (e.g., sustained increase in exercise and improved diet to reduce body mass index thereby reducing risk for type 2 diabetes), and health care use (e.g., whether knowing about increased risk results in an increase in visits to a physician). A primary difference between this study and the DTC information is the focused way in which this study vets genetic information and reports it to participants (Fig. 4). Only conditions

**Figure 3.** Workflow of the CUS being undertaken within the AFMS. Informed consent is obtained, and volunteers are given comprehensive questionnaires. Saliva is collected and assayed for genome-wide SNP variants. Risk reports are generated, and outcomes are evaluated. Outcome surveys are administered 3 months and then 12 months after a participant views their risk report to determine changes in behavior, health outcome, and risk perception and whom information was shared with. (Adapted with permission from Ref. 12.)

SNP variants from the human genome. Genomic information is obtained from a saliva sample using a SNP-typing chip in a Clinical Laboratory Improvement Amendments-certified laboratory. The Affymetrix Genome-Wide Human SNP Array 6.0 collects 906,600

**Figure 4.** Overall schematic of study infrastructure, workflow, and integration of new and continually reviewed literature for risk reporting. Literature is constantly curated until a case can be made for inclusion of a particular condition or drug variant for reporting in the study. This information is then reviewed by a panel of experts: the Informed Cohort Oversight Board (ICOB) considers complex conditions, and the Pharmacogenomics Advisory Group (PAG) considers drug variants for inclusion in the study. If approved, risk reports are developed, and the condition or drug variant is reported in study participants’ results. As new scientific literature emerges, new conditions/drug variants can be included in the study. In addition, those conditions/drug variants that are currently approved can be constantly re-evaluated and updated.
or pharmacogenomic variants that are actionable or preventable are reported, and those are vetted through a process of meta-analysis, oversight board selection, and risk reporting\textsuperscript{13, 14} described below and in Fig. 4. The CUS is being implemented through a partnership with the Coriell Institute for Medical Research (Camden, New Jersey) as part of their Coriell Personalized Medicine Collaborative. The Coriell Personalized Medicine Collaborative has developed and provides the genotyping infrastructure, risk report generation, genetic counseling services, surveys, and outcomes follow-up for the study.

Important to the implementation of genomic medicine is the determination of “actionable variants.” These are variants associated with a preventable, treatable, or manageable disease or condition and whose presence provides sufficient predictive capability to enable informed courses of action for provider and patient. Coriell has developed a process for condition/trait and actionable variant selection that uses a model first proposed in the journal Science by Kohane et al.\textsuperscript{13} First, the genetic variant and associated health condition are selected through a structured survey of the literature. A single variant is selected by conducting a meta-analysis of multiple studies to determine whether the variant has been replicated in multiple studies and within multiple cohorts within a single study. Second, the variant is assessed by an ICOB consisting of physicians, genomic scientists, and ethicists. The ICOB determines whether the variant and condition have sufficient evidence, actionability, and/or preventability. For pharmacogenomic drug/gene variant pairs, a PAG also assesses the utility of the selected information. Finally, a single publication is selected for risk reporting through a process of study quality assessment. Relative risk is then generated on the basis of the presence and type of variant, and the results are integrated into the participant report along with the other nongenetic risk factors (Fig. 5).

A list of currently approved conditions selected and reported through this process can be seen in Table 1. As the program develops, new conditions and variants are

\textbf{Figure 5.} Graphic of the web portal-based risk factor reporting of a chronic disease for the CUS. Relative risk for a particular genetic variant is only reported alongside other risk factors, such as family history, body mass index, and smoking status, which are determined from the detailed family history, lifestyle, and environmental questionnaires filled out by each participant. Educational materials are also embedded into the interface for each condition, and genetic counseling is available if requested. (Screenshot courtesy of the Coriell Institute for Medical Research.)
community via the National Institutes of Health Database of Genotypes and Phenotypes (dbGAP). Results from this study will be combined with knowledge generated from other studies and the overall community to inform the standard of care for AFMS.

### Long-Term Integration of PC2-Z Components into the Standard of Care for DOD Beneficiaries

The long-term goals of the PC2-Z program are to not only provide the evidence for genome-informed medicine, but also build the infrastructure for its usage. Each of PC2-Z’s pillar focuses has a long-term plan for integration into the clinical standard of care.

The research/knowledge generation implementation overview can be seen in Fig. 6. As genomics data are enabled by technologies such as SNP chips and whole-genome sequencers, the use of these data will need to be combined with clinical data and knowledge of care. The current model for establishing the utility of a genetic test involves evaluating the test’s analytical validity, clinical validity, clinical utility, and ethical/legal/social implications (collectively known as the ACCE model of clinical utility). Analytical validity is the ability of a genetic test to detect the presence or absence of a particular variant. Clinical validity is the ability of a particular test to predict the presence, absence, or risk of a particular disease by detecting the variant. Clinical utility describes how useful the test is in the prevention, diagnosis, and treatment of the disease. Across all of these, ELSIs will need to be kept in mind.

A big difference between a single genetic-variant diagnostic test and a genome-wide test is that a genome-wide test collects thousands to millions of variants. For clinical utility to be determined, each variant, disease,
and trait will have to be considered individually for their clinical utility. Therefore, the PC2-Z program envisions the development of a “clinically annotated genome,” which will report validated, clinically useful results for individual variants, traits, and diseases on a single, curated, genome test record.

Additional goals of the research/knowledge generation focus in PC2-Z are the development of a research biobank and ancillary studies of interest for the DoD. The biobank will make available samples and data to the broader research community. Ancillary and knowledge generation-studies will make use of the community cohort population, and genomic and health record data will be used for new genetic association studies if enough statistical power for a particular condition or trait is available. These data will contribute to the overall research knowledge base (Fig. 6) and eventually inform the standard of care for the PC2 program. The CUS being implemented by the PC2-Z program is a part of the broader strategy for implementation of genome-informed medicine in the standard of care. The ACCE model is a process for evaluating genetic tests developed by the Evaluation of Genomic Applications in Practice and Prevention Working Group organized by the Centers for Disease Control and Prevention Office of Public Health Genomics. The current study is evaluating SNP chip genome-wide screening done in a Clinical Laboratory Improvement Amendments-certified laboratory, and there are plans to go to whole-genome sequencing when feasible. After whole-genome sequencing is under way, it is envisioned that the diagnostics/screening portion of the system diagram would incorporate a clinically annotated genome for each individual.

A number of policy and operational challenges that interfere with the public’s ability to gain the benefits of personalized medicine through health information technology. These challenges include issues such as interoperability, inconsistent coding and language standards, problems in data sharing, weak feedback loops, privacy concerns, and ineffective reimbursement policies. Interoperability represents a major challenge because of the difficulty of integrating data from different sources. Researchers and health care providers not being able to exchange information raises the cost of health care and makes real-time learning difficult. A considerable amount of medical information is collected but too little of it is integrated or put into databases that are usable for research or public health purposes.

As our understanding of diseases becomes ever more stratified by their genomic signatures, even larger data sets will be needed to establish treatment protocols. Patient data across geography and health care plans will need to be queried simultaneously. The optimal utilization of these data can be achieved only through large, federated pools of information that includes patient genomic data and patient health histories. A key component of efforts in this area is focused on testing and evaluating how genomic information can be effectively and efficiently integrated into existing electronic health care records.

Genomic information can be voluminous and contain information that spans both medical and behavior characteristics. Issues of what information is collected and how it is stored and accessed will be addressed and appropriate protocols and procedures will be developed and used. Additionally, we are developing a learning information system that incorporates genomic data into existing and future DoD informatics tools. We will ultimately develop an advanced genomic diagnostic system prototype that supports delivery of full-sequence genomic information into the health system workflow and incorporates standards, ELSIs, patient rights, intellectual property, reimbursement, medical-legal documentation, interoperability across health systems, and regulatory requirements/FDA requirements.

The ELSI/policy research pillar poses unique challenges. The Human Genome Project and related ini-

Figure 6. Diagram of the integration of genomic (and any other ‘omic) data into the standard of care for the PC2 program. The CUS being implemented by the PC2-Z program is a part of the broader strategy for implementation of genome-informed medicine in the standard of care.
Innovative initiatives have introduced powerful new methods for studying genetics and lay the foundation for new approaches to the diagnosis and treatment of human disease. However, this progress in technology and translational medicine is accompanied by a myriad of important ELSIs. Although many of these issues are not unique to genomics (such as confidentiality, informed consent, discrimination, and stigmatization, etc.), they require a more focused consideration in the context of genomics. Genomics is unique in that genomic approaches introduce a new language of “probability” and “susceptibility” to health care and furnish information about disorders and diseases that often are of interest to third parties including families, governments, insurance companies, law enforcement, or scientific researchers. To address the potential for discrimination by employers or insurers seeking genomics information, the U.S. Congress enacted the Genetic Information Nondiscrimination Act (GINA) in 2008. This legislation was intended to break down potential barriers to the adoption of genomic medicine but is not fully protective for members of the U.S. military. The PC2-Z program recognizes that there will be a delicate balance of an individual’s right to privacy, operational readiness, and force health protection.

The education and coordination pillar addresses the lack of genetic and genomic education among not only patients and individuals but also providers. Issues surrounding responsibility for patient and provider education are currently being addressed by the genomic medicine community through the formation of cross-functional organizations such as the National Coalition for Health Professionals Education in Genetics, the Personalized Medicine Coalition, and the Genetic Alliance. These organizations have developed materials that will be adopted by the PC2 program to support AFMS educational initiatives. In addition, the CUS has been strategically targeted at the AFMS so that providers and support staff learn more about genomics by participating in the study. This pedagogical learning approach, which has been shown to be effective in the continuing medical education of physicians, has also been suggested as a model for educating providers on genetic medicine.18–20

The PC2-Z program is poised to address these many diverse needs and the ELSI challenges specific to the Military Health System. One of the key methods being used by the PC2-Z program to ensure consideration and incorporation of ELSI components is a policy-based requirements elicitation process implemented through a series of symposiums. The symposiums are used to help the PC2-Z program further explore the complexities of health care from a variety of perspectives that will ultimately help prepare the public, government, military, health care community, and policy makers for the coming revolution in personalized medicine. Outcomes from each symposium are subsequently being used to guide ongoing long-term program activities as well as to build a consortium of collaborators for ongoing and future program coordination.

Figure 7. System workflow diagram for integration of bioinformatics/clinical systems engineering into personalized medicine. New health data are captured and merged with existing health data, and research results are incorporated into the system by vetting through a DoD panel. This panel recommends protocols for the clinician and patient decision support platform, which would provide clinical diagnostic support. As clinicians implement this infrastructure, data are captured and analyzed by system tools that complete the cycle by informing the research community and the planning components of the system.
ANNUAL PERSONALIZED MEDICINE SYMPOSIUM

To ensure that the PC2-Z program was aware of and aligned with the current practices for genomic medicine and to further explore the complexities of preparing for and implementing genome-informed health care, in September 2011 APL conducted a one-day symposium entitled Changing the Health Care Paradigm. This symposium provided a unique opportunity for subject-matter experts to participate in critical discussions by using a “life-cycle” scenario to illuminate challenges faced by clinicians, patients, and policy makers related to the implementation of genome-informed health care. Attendees included experts from the clinical, research, ethical, legal, policy, genetic counseling, education, laboratory, insurance, and bioinformatics communities.

Lieutenant General (Dr.) Bruce Green, USAF Surgeon General (now retired), provided opening remarks that acknowledged that genome-informed medicine will become a critical component of state-of-the-art health care systems. Lt. Gen. Green further discussed the need for the USAF to be prepared to incorporate evidence-based, genome-informed patient information into the workflow of the AFMS. Major (Dr.) Cecili Sessions then provided an overview of the PC2-Z program to include the long-term vision. Mr. Joseph McInerney, from the National Coalition for Health Professionals Education in Genetics, facilitated discussion for the remainder of the day using the scenario-based modules. Figure 8 shows meeting participant responses to a selection of the questions posed during each module. These data were collected, along with overall e-chatter from the internal meeting chat board, for an overall representation of input from stakeholders at the meeting.

The discussions and survey results highlighted many exciting areas where genomic information has the potential to revolutionize health care. Overall it was clear that participants agreed more research and clinical studies are needed to better understand the clinical relevance and complex associations between genetic variants, medical and family histories, and environmental exposure conditions in order to fully realize the power of genomic data.
in evidence-based care. It was noted that the USAF and sister services are well-positioned to perform such studies because of the availability and consistency of the medical coverage and health care records for individuals and beneficiaries in the Military Health System. In summary, the outcomes from this symposium are being used to advise and influence the way forward for the PC2-Z program. The following is a list of high-level conclusions that encapsulate major discussion points from the event:

- A multitude of questions and issues remain to be resolved to effectively and efficiently incorporate genomic information into existing health care systems, including the AFMS.
- Many ideas and/or options exist for educating the health care community and the general public. However, little effort to provide this education has been actively implemented.
- It remains unclear where personal genomic data should be stored and how the data should be managed and kept secure. Consideration should be given to storing genome-based information in a secure, standardized data “warehouse.”
- The USAF is in a good position to conduct studies that may provide valuable data to ultimately support clinical implementation.
- Genomic-related initiatives will need to be flexible and have the capability to adapt to evolving science and technology.
- Information should be used for improving patient outcomes, prevention, and directed treatments.
- Genomic medicine should be fully integrated into medical care and be affordable and accessible to the health care team as well as the patient.
- Complete genomic screening of newborns and risk assessments will likely become standard.
- Actionable variants (possibly determined by a national committee) will need to be integrated into electronic medical records using decision support software for clinicians. Actionable variants will also need to be updated regularly as new information emerges.
- Clinicians will need to supplement a person’s genomic information with relevant ancillary information, such as medications, diet, and behaviors, to develop a strategy for health maintenance (or attainment).
- Ongoing clinical trials from biorepository specimens will be needed to generate new data.
- The insurance community could view genomic information as part of preventive care similar to annual physicals.

THE FUTURE OF GENOME-INFORMED MEDICINE

At the conclusion of the symposium, participants were asked to comment on what they believed genomic medicine would look like in 15 years “in a perfect world.” Many participants felt genomic medicine would be more fully integrated into the health care system, enabling it to provide truly personalized health care. Several participants expressed the belief that ultimately, a full genome sequence would be generated shortly after birth as a standard of care and deposited in a secure data warehouse. A national committee would be in place to review and set actionable genetic variants to be forwarded to electronic medical records. These variants and new markers would be continuously reviewed in light of new research, and alerts could be generated to signal changes and updates. Participants also felt that information would be used to personalize pharmaco genomics (i.e., predict who is at risk for harmful side effects and personalize dosing regimens) and tailor personalized treatment, monitoring, and preventive health care plans. Additional thoughts included the likelihood that sequencing of tumor cells in an oncology setting will allow individualized targeted therapies.

CONCLUSION

Technology is making genome-informed care a reality, and the national infrastructure needs to be developed to support it. The PC2-Z program is the first attempt by the USAF to build that infrastructure. PC2-Z will pave the way for such care for all DoD personnel by addressing the scientific/medical, informatics, policy, and educational issues that need to be addressed before genome-informed care can become a reality. The program is scalable and responsive to the inclusion of new ‘omics and medical data and will serve as a translational resource to take proactive advantage of the genomic revolution, instead of being surprised by it.

The PC2-Z experience and infrastructure will eventually be implemented by all the services, and federal, military, and academic stakeholders are helping to guide program goals, ethics, and policies throughout the program. PC2-Z bioinformatics/clinical systems engineering efforts are developing the military electronic health record infrastructure, and organizations that provide educational materials are also integral and engaged. Finally, the CUS will provide initial experience with genome-wide information obtained by SNP-typing technology, and then with whole-genome sequence a few years into the study. By that time, the road to genome-
informed personalized medicine for the military will be well under way as the genomic revolution develops.

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